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Review Article

Phytochemical and Pharmacological Accounts of Some Reviewed Plants with Antidiabetic Potential

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Abstract: With increased morbidity and mortality, diabetes mellitus is emerging as major health problem. 69% adults of developing countries and 20% of developed countries are susceptible to diabetes. Insulin therapy is suggested only when diet or oral hypoglycemic fails to control blood glucose levels and in case of postpancreatectomy. Insulin analogues are advantageous with low risk of hypoglycemia particularly nocturnal hypoglycemia. Drawbacks of insulin therapy are like local pain, inconvenience of multiple injections, insulin edema, lipohypertropy, insulin allergy, resistance and above all of this are weight gain. Oral hypoglycemic agents like Sulphonylureas (Glibenclamide, Glipizide, Gliclazide), Non-Sulphonylureas (Nateglinide, Repaglinide), Alpha-glucosidase inhibitors (Acarbose, Miglitol), Dipeptidylpeptidase(DPP) IV inhibitors (Sitagliptin, Linagliptin, Alogliptin, Dutogliptin, Gemiglaptin) are used for treatment of diabetes but they have their own limitations due to selective mechanism of action. WHO in 1976 officially recognized importance of traditional medicine as source of primary health care by globally addressing its traditional medicine programme. India being the botanical garden of the world, is the largest producer of medicinal herbs. 21,000 plants are listed by WHO, used for medicinal purposes around the world. This review covers phytochemical and pharmacological accounts of some plants with antidiabetec potential. Herbal drugs are the oldest known healthcares available to mankind, enlisted in naturopathic, ayurvedic, homeopathic and other medicine systems obtained from natural sources. Herbal drugs becomes advantageous over allopathic drugs due to their safety, low cost, complete accessibility with enhance tolerance.There is more preclinical research warranted for exploration of antidiabetic potential of new plants/herbs whichever is not yet studied and there is also need of clinical establishment of antidiabetic plants which are already found promising in their preclinical evaluation.
Keywords: diabetes mellitus, Oral hypoglycemic agents, phytochemical, Herbal drugs

INTRODUCTION

Diabetes Mellitus (DM)

As per WHO diabetes mellitus referred as diabetes, characterized by hyperglycemia is a chronic disease, which occurs when pancreas produces insufficient insulin or there is decreased insulin sensitivity in cells [1, 2] by the year 2025,300 million people worldwide will be affected by most common endocrine disorder i.e. diabetes [3]. 69% adults of developing countries and 20% of developed countries are susceptible to diabetes [4]. With increased morbidity and mortality, diabetes mellitus is emerging as major health problem [5-7].

Types of DM

Type -I or Insulin Dependent Diabetes Mellitus (IDDM)/ juvenile-onset /ketone-prone diabetes

It is immune mediated or idiopathic diabetes mellitus, characterized by destruction of beta cells of pancreas by T- cell mediated immune attack and life span of pancreatic cell is decreased by one third along with ketoacidosis in body tissues and fluid [1, 4, 8].

Type-II or Non-insulin Dependent Diabetes Mellitus (NIDDM)/ adult-on-set diabetes

Lack of insulin secretion in response to blood glucose levels demonstrates NIDDM. Reduced insulin sensitivity is predominant abnormality, leading to hyperglycemia which can be reversed by drugs improving insulin sensitivity or reducing glucose production by liver [1, 8].

Gestational Diabetes Mellitus (GDM)

In a non-diabetic pregnant woman, gestational diabetes develops near the end of the 3rd trimester or beginning of 4th trimester. It is characterized by carbohydrate intolerance due to body's inability to use

insulin as a result of pregnancy induced hormonal changes. 4% of pregnancies are affected by gestational diabetes, which disappears after child birth [3, 9, 10].

TREATMENT OF DIABETES MELLITUS

Allopathic treatment (insulin therapy)

Insulin

It is an endocrine hormone released from β cells of pancreas, obtained from biological origin and classified as rapid acting, short acting, intermediate acting or long acting. In 1992, insulin was introduced for clinical use before each main meal and one injection in the night, usually at 1 a.m. insulin is a small protein with a molecular weight of 5808. It contains 51 amino acids arranged in two chains A and B linked by disulphide bridges [11-14].

Pharmacodynamics of Insulin

Initial dose: 0.5-1.0 units/ kg per day and maintenance dose Adjust doses to achieve premeal and bedtime glucose level of 80-140 mg/dl. Insulin facilitates glucose entry into adipose tissues, muscles, and liver by stimulating several enzymatic reactions that start at the insulin receptors. The stimulation of an intrinsic tyrosine kinase of the insulin receptor results in an increase in membrane phosphorylation that consequently increases the membrane permeability to glucose through a complicated cascade of intracellular events and by inhibiting hepatic glucose production [13,15].

Table 1: Pharmacokinetics of Insulin [15]

Biosynthesis and release	Distribution.	Metabolism	Excretion
Proinsulin is precursor of insulin, biosynthesized in pancreas and certain proteolytic enzymes breaks down it into active form i.e. insulin.	Insulin doesn't shows plasma protein binding, hence it is rapidly distributed throughout the extracellular fluid, once releases from pancreas.	Liver is a principle site for insulin metabolism where aspartially it is metabolized in muscles tissues and kidneys. With a short half life (about 5-6 minutes), 50% of circulating insulin is deactivated by the liver.	About 98% of unchanged insulin is reabsorbed in the proximal tubules for further action.

Advantages and disadvantages of Insulin

Insulin therapy is suggested only when diet or oral hypoglycemic fails to control blood glucose levels and in case of postpancreatectomy. Insulin analogues are advantageous with low risk of hypoglycemia particularly nocturnal hypoglycemia. Drawbacks of insulin therapy are like local pain, inconvenience of multiple injections, insulin edema, lipohypertropy, insulin allergy, resistance and above all of this are weight gain [15-18].

ALLOPATHIC TREATMENT (ORAL HYPOGLYCAEMIC THERAPY)

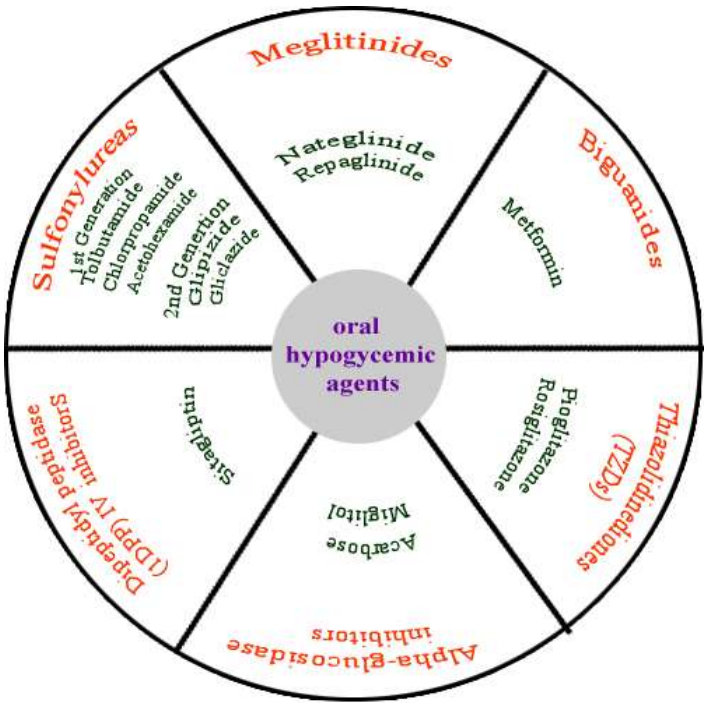


Fig. 1: Classification of allopathic antidiabetic medicines

Sulphonylureas

Sulphonylureas derivatives of sulfonic acid and urea, are time tested oral hypoglycemic from last 50 years [19, 20] Second generation (Glibenclamide, Glipizide, Gliclazide) sulphonylureas are clinically used today were as First generation(Tolbutamide, Chlorpropamide, Acetohexamide, Tolazamide) sulphonylureas is outdated [21, 22].

Non-Sulphonylureas

(Meglitinides)Nateglinide and Repaglinide represents non sulphonylureas as meglitinides where former isbenzoic acid derivatives and later is phenylalanine derivatives [23].

Alpha-glucosidase inhibitors

Acarbose and Miglitol are luminally acting oral hypoglycemics acts by inhibiting enzyme Alpha-glucosidase [22].

Dipeptidylpeptidase (DPP) IV inhibitors

Sitagliptin and linagliptin are worldwide registered DPP-IV inhibitors. Alogliptin, dutogliptin, and gemiglaptin, are recently developed [24].

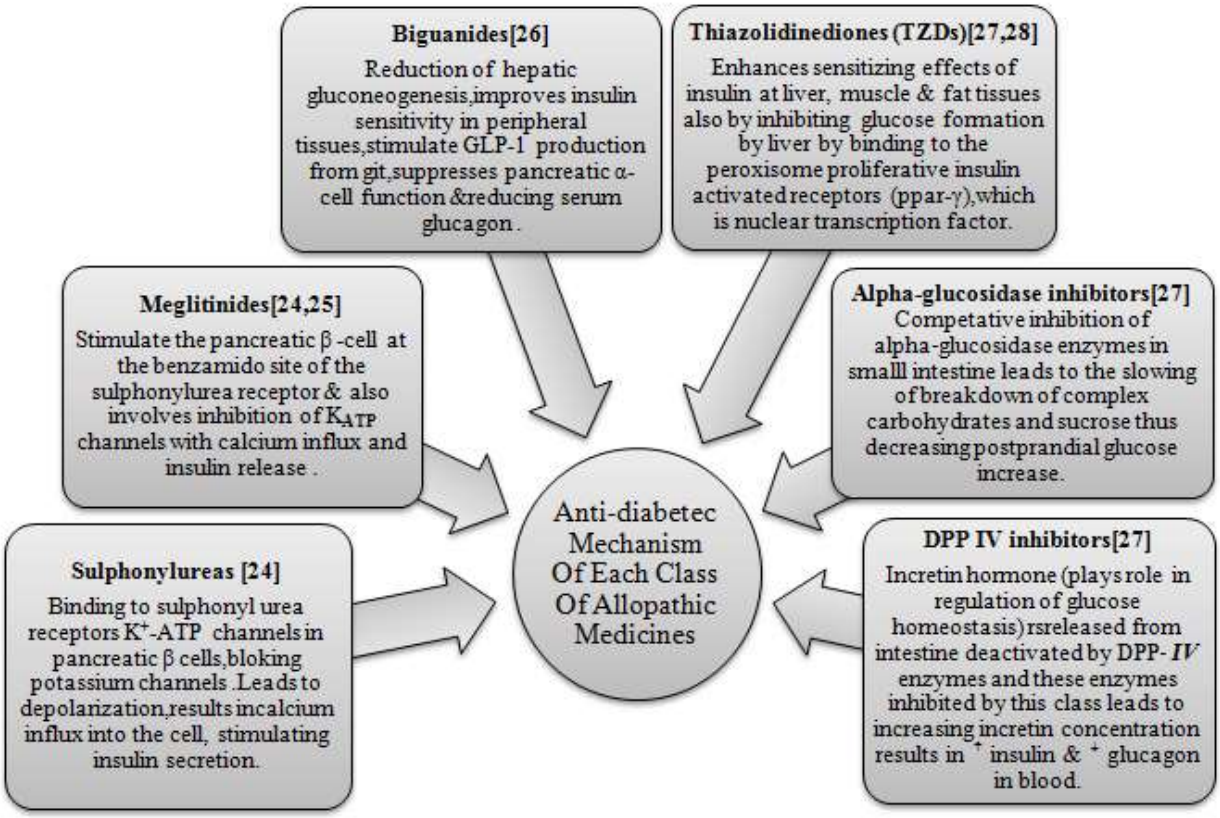


Fig. 2: Antidiabetec Mechanism of Allopathic Medicines

Table 2: Simplified comparative data of oral hypoglycemic agents [3,4,13,27]

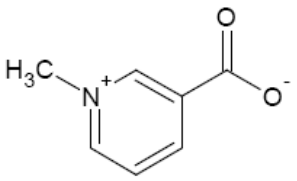
DRUG CLASS	Individual drugs	Dose of drugs(mg/day)		Advantages	Disadvantages	Most common ADR
		Initial dose	Maintainance dose			
Sulfonylureas	Acetohexamide	250	1500	Inexpensive, improved lipid profile by lowering Triglycerides	Weight gain, and rarebut severe hypoglycemia	Hypoglycaemia, Rare allergies, SIADH can be caused by first generation and disulfiram reaction with alcohol, cardio-vascular effects
	Glipizide	5	20			
	glyburide	2.5	08			
	Glimepride	1-2	-			
(Meglitinides)	Nateglinide	180-480	120	Lower triglycerides,	Weight gain similar to	Experience limited, hypersensitivity

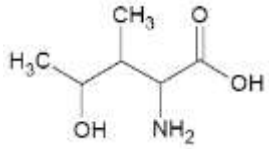
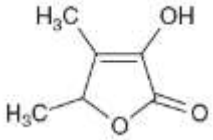
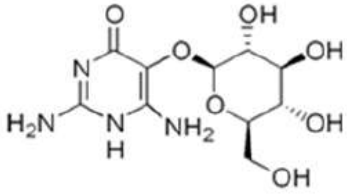
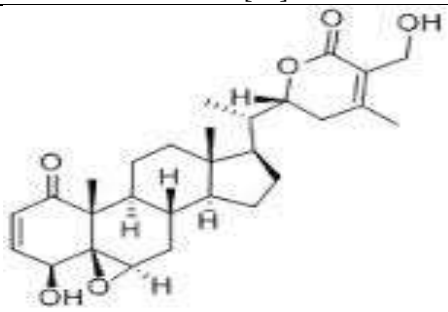
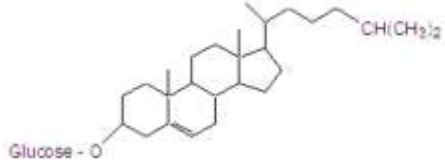
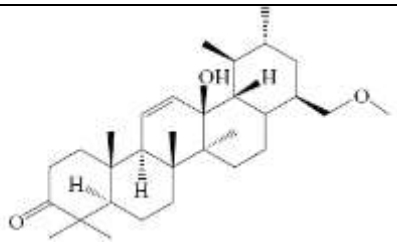
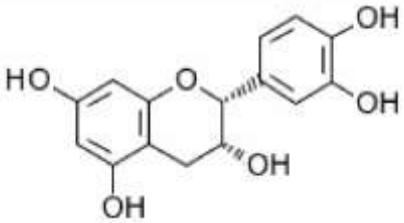
	Repaglinide	0.5-2	16	uncommon hypoglycemia	hypoglycemia	reactions including pruritus, rashesandurticaria.
Biguanides	Metformin	500mg b.i.d	2550	Metformin is only FDA approved oral diabetic in children more or =to 10 years. Lowers TG and total cholesterol, No hypoglycemia, No weight gain	Minimal effect on HDL, used as monotherapy does not sustain HbA1C reductions	Gastrointestinal side effect (Diarrhea) minimized by XR form. Lactic acidosis occurs rarely , abdominal discomfort, and metallic taste
Thiazolidinediones (TZDs)	Pioglitazone	15-30	45	Lower TG, and raises HDL, No hypoglycemia effect	Weight gain, elevated ALT levels, and edema noted.	Gastrointestinal adverse effects at elevated dosages, rare liver failure,
	Rosiglitazone	4-8	8mg/day or 4mg b.i.d			
Alpha-glucosidase inhibitors	Acarbose	NA	25-100mg t.i.d	Lower TG, No hypoglycemia noted, as well as absence of weight gain	Minimal effect on total cholesterol andHDL levels	Gastrointestinal adverse effects such as bloating, and flatulence.
	Miglitol	NA	25-100mg t.i.d			
Dipeptidyl Peptidase (DPP) IV inhibitors	Sitagliptin	NA	100mg once with/ without food	Neutral effect On weight, No hypoglycemia, No drug interactions	Minimal effect on total cholesterol and HDL	Upper respiratory tract infection, headache.

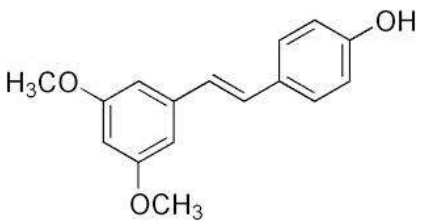
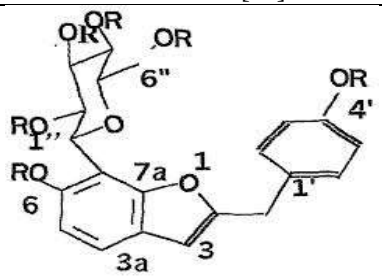
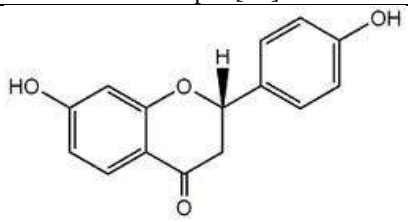
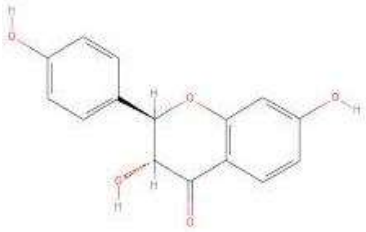
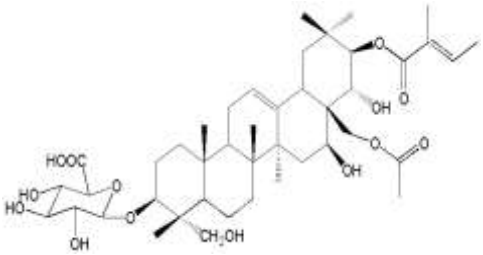
TRADITIONAL & ANCIENT USE OF ANTIDIABETIC HERBAL MEDICINES

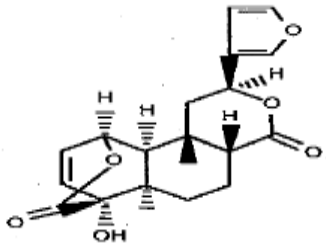
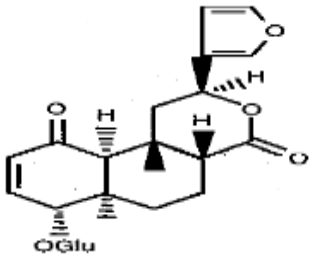
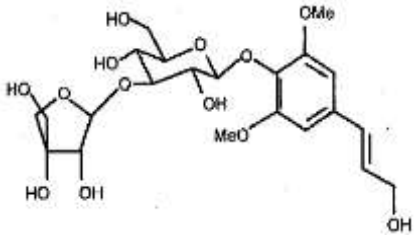
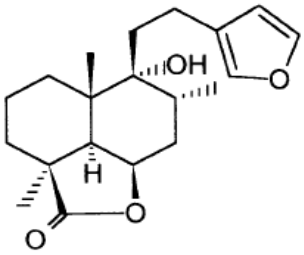
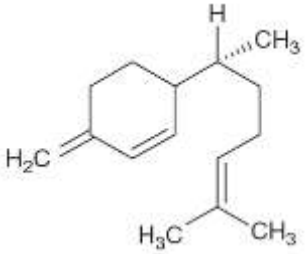
WHO in 1976 officially recognized importance of traditional medicine as source of primary health care by globally addressing its traditional medicine programme [29]. India being the botanical garden of the world, is the largest producer of medicinal herbs. 21,000 plants are listed by WHO, used for medicinal purposes around the world [30]. This review covers phytochemical and pharmacological accounts of some plants with antidiabetec potential. Herbal drugs are the oldest known healthcares available to mankind, enlisted in naturopathic, ayurvedic, homeopathic and other medicine systems obtained from natural sources. Herbal drugs becomes advantageous over allopathic drugs due to their safety, low cost, complete accessibility with enhance tolerance [31].

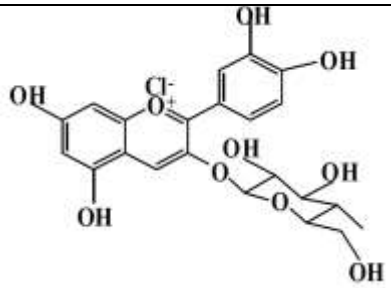
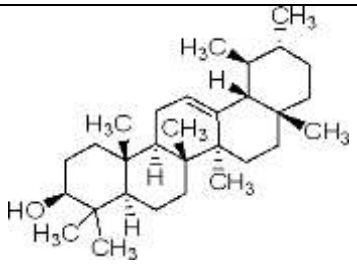
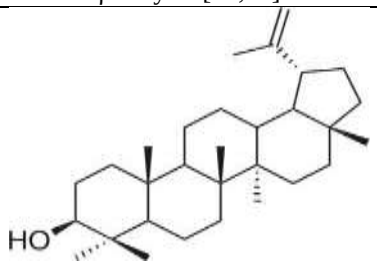
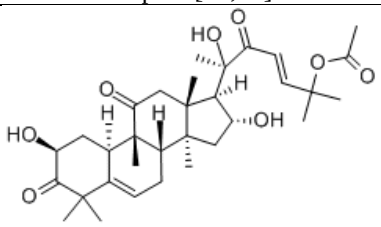
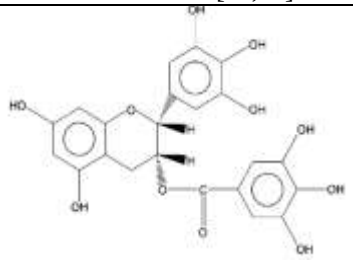
Table 3: Phytochemistry of herbal antidiabetic medicinal plants

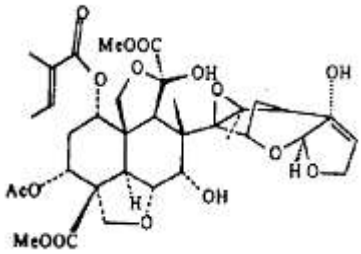
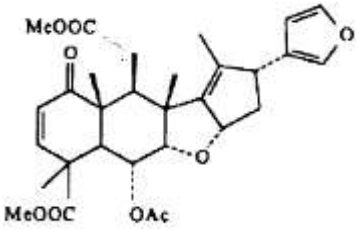
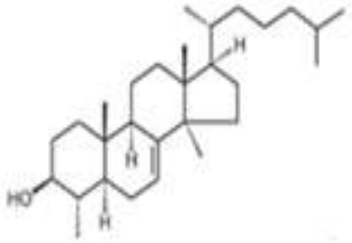
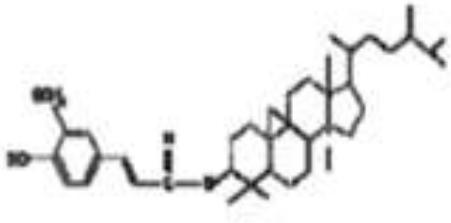
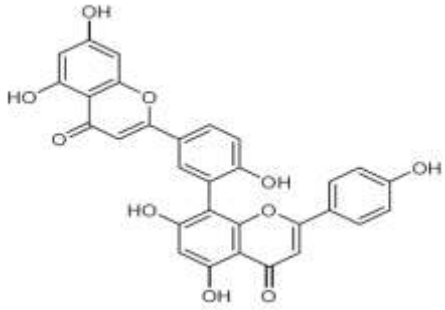
Botanical name of plant	General (local) name	Plant part used	Active (antidiabetec) chemical constituents with their structure
Trigonellafoenum graecum [32]	Methi [33] Fenugreek [34] (English vernacular)	Seeds [33]	 Trigonelline (1-methylpyridinium-3-carboxylate) [35-36]

			 4-hydroxyisoleucine (2-amino-4-hydroxy-3-methylpentanoic acid)[35,36]
			 Sotolon [35,37]
			 Vicine [38]
			 withaferin-A [38]
Momordica charntia [39] 	Bitter gourd, Balsam pear, Bitter melon, Bitter cucumber [40]	Fruits, seeds [39]	 Charantin [39,41]
			 Momordicin [42]
Pterocarpus marsupium [43]	Indian kino, Bijasal [43]	Heart wood, leaves, flowers, bark, & gum [44]	

			(-)-Epicatechin [45]
			 Pterostilbene [46]
			 Marsupin [47]
			 Liquiritigenin [47]
			 Isoliquiritigenin [47]
Gymnema sylvestre [48] 	Gurmar, mera-singi [48]	Leaves [49]	 Gymnemic acid [50]

Tinospora cordifolia [51] 	Guduchi, Giloy or Amrita [51]	Stem [52]	 Columbin [53]
			 Tinosporaside [53]
			 Cordifolioside A [53]
Marrubium vulgare L. [54] 	Horehound [54]	Leaf, roots [39]	 Marrubiin [39,55]
Zingiber officinale [56] 	Ginger [56], Adark [57]	Rhizome [57]	 Sesquiterpene [37,57] (β-Sesquiphellandrene)

*Grewiaasiatica*L.[58] 	Phalsa [58]	Fruit[58]	 cyanidin 3- glucoside [59,60]
Cocciniaindica [61] (Cocciniagrandis, Cocciniacordifolia) 	Kundaru Ki Bel (Hindi) Ivy Gourd (English) [61]	Fruit, leaf, root, whole plant [62]	 β-amyrin [44,63]
			 Lupeol [44,63]
			 cucurbitacin B [44,63]
Camellia sinensis(L.) [64] 	Chha [64]	Leaf [65]	 Epigallocatechingallate [66,67]

Azadirachtaindica [68] 	Neem [68]	Bark, Leaf, Seed [62]	 Azadirachtin [68,69]
			 Nimbin [69,70]
Aloe vera [71] 	Goddess, Kumari, Guarpatha [71]	Leaves [72]	 Lophenol (phytosterols) [73]
			 4-Methylenecycloartanol [73]
Biophytumsensitivum [74] 	Life plant, little tree plant, sensitive plant [74]	Leaves [75]	 Amentoflavone [76,77]

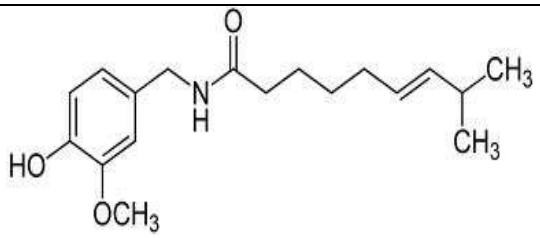
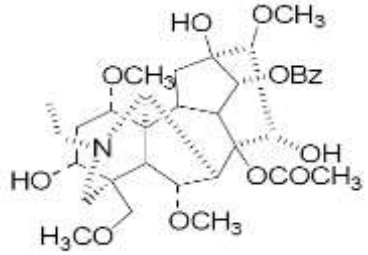
Capsicum annum [78] 	Chilli pepper[78]	Fruit [78]	 Capsaicin[79,80]
Acontium carmichaeii [78] 	Pinyn [78]	Root [78]	 Aconitine [81,82]

Table 4: Mechanism of action, available dose and dosage form of antidiabetic plants

Plant name	Antidiabetic mechanism of action	Dose	Dosage form
Trigonellafoenum graecum	It diminishes the carbohydrate metabolism by inhibiting intestinal enzyme alpha-amylase. It stimulates glucose dependant insulin secretion from pancreatic beta cells to induce hypoglycemia.[83]	10-15 grams per day in divided doses with meals. [35]	Seed powder. [83]
Momordica charntia	It mimics insulin activity by stimulating muscle cells glucose and aminoacid uptakes, decreases hepatic gluconeogenesis. [84, 85]	Fresh juice- 57-113 gm daily, Tincture- 1.3 ml/ twice/ daily, Juice extract- 300-600 mg.[10]	Crude drug, extracts, fruit juice and tablets.[77]
Pterocarpus marsupium	It exerts protective, restorative, regenerative effects in diabetic beta cells. Insulin releasing activity is correlated to potential increase in the cyclic adenosine monophosphate (cAMP) in pancreatic islets, along with significant convertion of proinsulin to insulin [86]	Wood extract (pterostilbene) – 10 mg/ kg, Bark decoction- 1 gm/ 100 mg body weight for 10 days [10]	The wood extract & bark decoction [10]
Gymnema sylvestre	Hypoglycemic activity of gymnemic acid isdue to regeneration of islet cells, stimulation of insulin release , increase glucose uptake by cells, inhibition of glucose absorption, and suppression of gluconeogenic enzymes and sorbitol dehydrogenase [87]	Powder leaf- 2-4 mg/daily, Water soluble acidic solution- 400 mg/day [10]	It is used as water soluble acidic solution &as powered leaf [10]

Tinospora cordifolia	Decreased blood glucose by level and increased glucose tolerance is correlated with regeneration of beta cells of islets of langerhans [88]	aqueous extract at a dose of 400 mg/kg,its effect is equivalent to only one unit/kg of insulin [89]	the hydro alcoholic and chloroform extract of t.cordifolia stem [90]
Marrubium vulgare L	Promotes insulin release from beta cells of islets of langerhans or and inhibit processs of insulin breakdown [91]	the aqueous extract at 200 and 300 mg/kg/ twice daily for 2 weeks [91]	Decoction.[92]
Zingiber officinale	By improving insulin sensitivity it reduces fasting blood glucose and improves serum insulin level [65]	3–10 g fresh ginger, or 2–4 g dry ginger, 1–3 ×/day [93]	Fresh ginger juice [93]
*Grewia asiatica*L	Hypoglycemic effect is mainly result of improving glucose utilization by cells [94]	1 kg sugar, 1 glass of water and 2 teaspoon of ghee are heated to make sheera. Then 1 kg crushed fruit of Grewiais mixed with it and strained through a fine cloth. 2-3 teaspoon strained mixture is used With one glass of water twice a day [95]	Syrup (One kg fruit is crushed with fingers in 1 liter of water and then strained. Sugar is added to the strained juice to make syrup. The syrup is taken according to the need) [95]
Coccinia indica	Glucose synthesis is inhibited by suppression of gluconeogenic enzymes like glucose-6- phosphatase and fructose-1, 6-bisphosphatase. Activates glucose-6-phosphate dehydrogenase thre by promoting glucose oxidation. Hypoglycemic effect is also due to insulin secretagogue activity [96]	Dried extract (500 mg/kg p.o., for 6 weeks), 3–6 g powder of Whole plant and 5–10 ml juice [96]	Bimb or Kanturi [97]
Camellia sinensis(L.)	Inhibits development of insulin resistance, hypoglymia and other metabolic effects .also decreases glucose absorption from intestine [64, 98]	1.5 g/body of green tea promoted glucose metabolism in healthy human volunteers [99]	Tea [97]
Azadirachta indica	Improves peripheral glucose uptake by inhibiting action of epinephrine on glucose metabolism [100]	Aq. Leaf extract is taken at a dose of 2-3 tea spoons daily in empty stomach.[68] and Capsule- 1-2 capsules/ twice daily [10]	decoction and juice of leaves[101] & capsules [10]
Aloe vera	Maintains glucose homeostasis by interfering with carbohydrate metabolizing enzymes. Increases production and release of insulin [44]	Aloe vera gel at 200 mg/kg possesses significant antidiabetic activity[102]	gel extract [71]
Biophytumsensitivum	Possess insulotrophic effects i.e. improvement in synthesis and release of insulin from the beta cells of langerhans [89]	200 mg/kg body weight is optimum for hypoglycaemia [89]	-
Capsicum annum	Insulin producing cells are protected from autoreactive T cells. Anti-inflammatory effects of capsaicin results due to binding of capsaicin to the VR1 receptors which activates pancreatic macrophages [103]	1g and 2g Capsicum frutescence supplemented diet [104]	-
Acontium carmichaeii	Improvement in peripheral glucose uptake is due to activation of opioid μ receptors of peripheral tissues, thereby lowering plasma glucose levels [81]	-	-

CONCLUSION

Biologically obtained insulin, insulin analogues and oral hypoglycemic agents are used for treatment of diabetes but they have their own limitations due to selective mechanism of action. India being the botanical garden of the world, is the largest producer of medicinal herbs. 21,000 plants are listed by WHO, used for medicinal purposes around the world. This review covers phytochemical and pharmacological accounts of some plants with antidiabetec potential. Herbal drugs are the oldest known healthcares available to mankind, enlisted in naturopathic, ayurvedic, homeopathic and other medicine systems obtained from natural sources. Herbal drugs becomes advantageous over allopathic drugs due to their safety, low cost, complete accessibility with enhance tolerance. There is more preclinical research warranted for exploration of antidiabetic potential of new plants/herbs whichever is not yet studied and there is also need of clinical establishment of antidiabetic plants which are already found promising in their preclinical evaluation.

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